Safety evaluation of long-term recombinant growth hormone treatment in childhood: interim analysis of the NordiNet® International Outcome Study

1. **Lars Sävendahl**
Karolinska Institutet, Stockholm, Sweden
2. **Effie Pournara**
Novo Nordisk Health Care AG, Zurich, Switzerland
3. **Tilman R Rohrer**
Saarland University Medical Centre, Homburg/Saar, Germany
4. **Birgitte Tønnes Pedersen**
Novo Nordisk A/S, Søborg, Denmark
5. **Marja-Terttu Saha**
Tampere University Hospital, Tampere, Finland
6. **Oliver Blankenstein**
Charité-University Medicine Berlin, Berlin, Germany

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Introduction

- Nearly 30 years' experience of growth hormone (GH) substitution has established a favourable safety profile;[1,2] however, theoretical concerns have linked excess GH and GH substitution with increased morbidity and mortality.[3–6]
- We present long-term safety data for 15,067 paediatric patients enrolled in the non-interventional, observational NordiNet® International Outcome Study (IOS), and treated with GH (Norditropin® [somatropin; recombinant GH], Novo Nordisk A/S, Denmark) between 1998 and 2014 at the discretion of their physician.

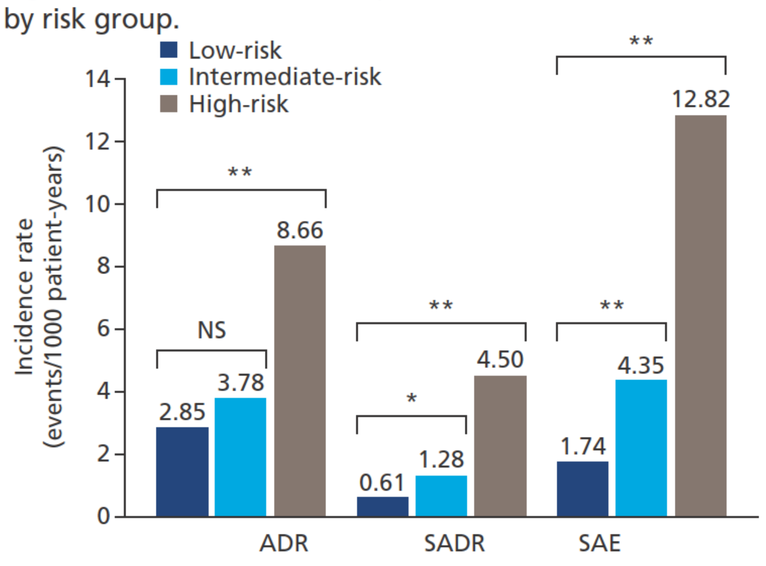
Methods

- Patients' diagnoses were classified according to the International Classification of Diseases 10th Revision criteria.[7]
- Based on the Safety and Appropriateness of Growth hormone treatments in Europe (SAGhE) study methodology, patients were classified into one of three categories according to clinical diagnoses at the start of GH treatment and the associated risk for long-term morbidity and mortality.[5]
- The risk groups comprised:
  - Low-risk: patients with isolated GH deficiency (GHD), idiopathic short stature (ISS), short children born small for gestational age (SGA), or children with isolated GHD in association with minor craniofacial malformation, such as cleft lip.
    - This group was further subdivided into GHD/ISS or SGA.
  - Intermediate-risk: patients with multiple pituitary hormone deficiency, defined paediatric syndromes known to be associated with increased mortality risk (e.g. Turner syndrome, Prader–Willi syndrome), benign pituitary tumours, severe craniofacial or other malformations, or severe or chronic paediatric disease.
  - High-risk: patients previously treated for cancer, craniopharyngioma or chronic renal insufficiency.
- Safety evaluation was based on physicians' reporting of adverse drug reactions (ADRs), serious ADRs (SADRs) and serious adverse events (SAEs).
- ADRs, SADRs and SAEs were coded in the Medical Dictionary for Regulatory Activities terms (version 14.0) using the Systems Organ Class terminology.
- The occurrence of neoplasms/malignancies/cardiovascular events/nervous system disorders were evaluated for patients in the low-risk group.

Statistical analysis

- Patient-years of exposure were calculated from start of GH treatment until the end of GH treatment, or the patient's last visit.
- Mean GH dose until the first event occurred (event defined as ADR, SADR or SAE) was considered clinically relevant as opposed to the mean dose throughout the whole treatment period. Mean dose (µg/kg/day) was stratified into four groups (% patients): 0–20 (4.6), 20–30 (27.2), 30–40 (46.5) and >40 (21.6).

Figure 1 Incidence rates of reported ADRs, SADRs and SAEs by risk group.



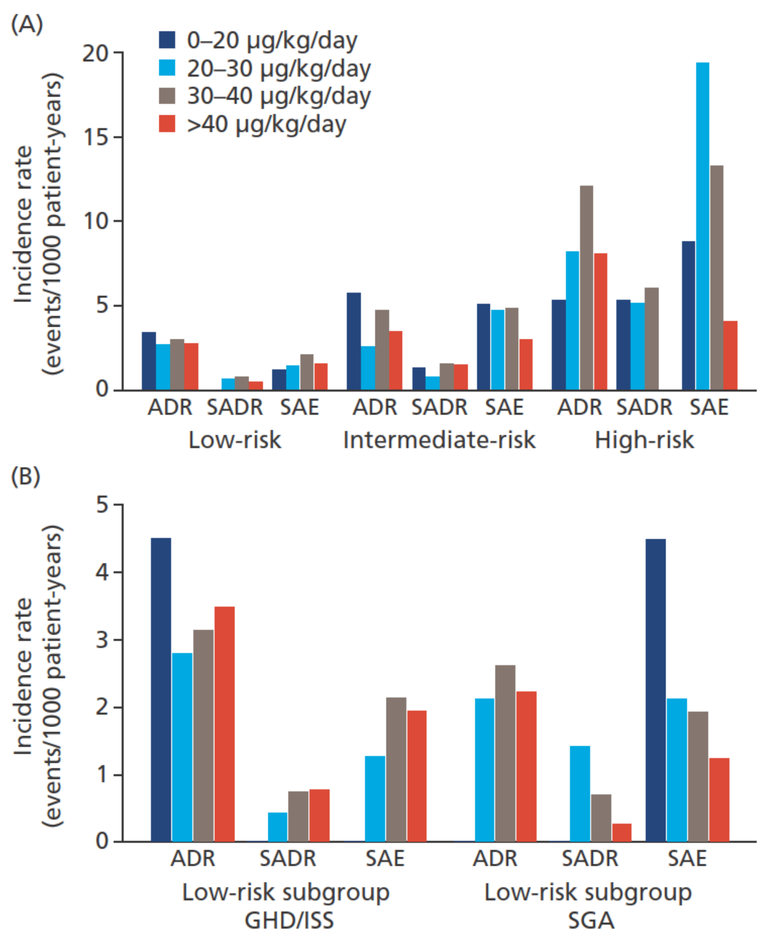
*p=0.0101, **p<0.0001 versus low-risk group.
ADR, adverse drug reaction; SADR, serious adverse drug reaction; SAE, serious adverse event.

- Incidence rates (IRs) for ADRs, SADRs and SAEs (events/1000 patient-years) were calculated by risk group and by mean GH dose until the first event. Comparison of IRs by risk group (low-risk group as reference) and mean GH dose until the first event were performed using Poisson regression (log-linear model), with mean GH dose until the first event as a continuous explanatory variable for the latter.
- Occurrence of neoplasms/malignancies/cardiovascular events/nervous system disorders in patients in the low-risk group were analysed descriptively.

Results

- Baseline demographics are displayed in Table 1.
- Mean GH dose until the first event was lowest in the high-risk group (Table 1).
- In total, 342 events were recorded in 297 patients, of whom 41.1% (n=122), 44.1% (n=131) and 14.8% (n=44) were in the low-risk, intermediate-risk and high-risk groups, respectively. Of all reported events, 63 were assessed as SADRs, 133 as SAEs and 146 events were assessed as ADRs.
- IRs for ADRs, SADRs and SAEs (p<0.0001) in the high-risk group, and SADRs (p=0.0101) and SAEs (p<0.0001) in the intermediate-risk group, were significantly higher versus the low-risk group (Figure 1), although similar between the GHD/ISS and SGA subgroups (3.13, 0.61, 1.73 vs. 2.38, 0.61, 1.77, respectively).
- No association was found between IRs for ADRs, SADRs or SAEs and GH dose until the first event in any of the risk groups/subgroups (Figure 2).
- Following an event, GH dose remained unchanged for 47.4% of patients, was reduced for 3.8% and discontinued for 26.9%. Action taken with GH dose after event onset was unknown for 21.9% of patients.

Figure 2 Incidence rates for reported ADRs, SADRs, and SAEs by GH dose until the first event across risk groups (A) and in subgroups of the low-risk group (B).



Analysis of incidence rates by mean GH dose until the first event using Poisson regression (log-linear model) with GH dose until the first event as a continuous variable: p=NS for all – ADRs: low-risk group p=0.98; intermediate group p=0.82; high-risk group p=0.29. SADRs: low-risk group p=0.60; intermediate group p=0.46; high-risk group p=0.33. SAEs: low-risk group p=0.81; intermediate group p=0.11; high-risk group p=0.46. ADR, adverse drug reaction; GH, growth hormone; GHD, growth hormone deficiency; ISS, idiopathic short stature; SADR, serious adverse drug reaction; SAE, serious adverse event; SGA, small for gestational age.

- Five neoplasms/malignancies/cardiovascular events/nervous system disorders were reported in five patients in the low-risk group:
  - One case each of benign oral neoplasm, benign intracranial hypertension and hypotension (with abdominal distension); assessed as possibly related to GH treatment (symptoms abated on discontinuation).
  - One case each of brain neoplasm and T-cell lymphoma; considered unlikely to be related to GH treatment.

Table 1 Baseline demographics.

	Low-risk			Intermediate- risk	High-risk	Overall
	Total low-risk cohort	GHD/ISS subgroup	SGA subgroup			
Number of patients (%)	9269 (61.5)	5784 (62.4)*	3485 (37.6)*	4992 (33.1)	806 (5.3)	15067 (100.0)
Sex, male/female, %	62.5/37.5	67.4/32.6	54.4/45.6	46.7/53.3	57.4/42.6	57.0/43.0
Mean age at treatment start, years (SD)	8.77 (3.65)	9.30 (3.77)	7.89 (3.26)	8.34 (4.25)	10.15 (3.91)	8.70 (3.89)
Height SDS at baseline (SD)	–2.61 (0.91)	–2.48 (0.93)	–2.81 (0.85)	–2.58 (1.28)	–2.00 (1.29)	–2.57 (1.07)
Mean duration of GH treatment, years (SD)	3.71 (2.72)	3.70 (2.73)	3.73 (2.71)	4.55 (3.16)	3.58 (2.65)	3.99 (2.90)
Average GH dose until first event, µg/kg/day (SD)	34.63 (8.68)	32.47 (6.79)	38.54 (10.31)	33.71 (11.60)	29.97 (10.00)	33.53 (10.33)

*Percentage of low-risk cohort.
GH, growth hormone; GHD, growth hormone deficiency; ISS, idiopathic short stature; SD, standard deviation; SDS, standard deviation score; SGA, small for gestational age.

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Conclusions

- Data from NordiNet® IOS further support a favourable safety profile for GH therapy in children.
- Patients who are considered to be at high risk of morbidity and mortality are more likely to experience an event (ADR, SADR or SAE) while on GH therapy than those at low risk.
- Within the dose range observed in this real-world study reflecting usual clinical practice, no association between GH dose during GH treatment and the occurrence of events during GH therapy was revealed.

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